

TRANSMITTAL LETTER TO THE UNITED STATES

NOV 15 2007
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

60132-083

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

C9/980836

INTERNATIONAL APPLICATION NO.

PCT/US00/16795

INTERNATIONAL FILING DATE

16 JUNE 2000 (16.06.00)

PRIORITY DATE CLAIMED

18 JUNE 1999 (18.06.99)

TITLE OF INVENTION

SIMULTANEOUS IMAGE ACQUISITION USING MULTIPLE FLUOROPHORE PROBE DYES

APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ has been communicated by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☐ Other items or information:

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PCT/US00/16795

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24. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **\$1040.00**
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **\$890.00**
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **\$740.00**
- ☒ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **\$710.00**
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **\$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =**\$710.00**Surcharge of **\$130.00** for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)).☐ 20 ☐ 30**\$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	14 - 20 =	0	x \$18.00	\$0.00
Independent claims	2 - 3 =	0	x \$84.00	\$0.00
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	\$0.00

TOTAL OF ABOVE CALCULATIONS =**\$710.00**

- ☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.

\$0.00**SUBTOTAL =****\$710.00**Processing fee of **\$130.00** for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)).☐ 20 ☐ 30**\$0.00****TOTAL NATIONAL FEE =****\$710.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

☐**\$0.00****TOTAL FEES ENCLOSED =****\$710.00**

Amount to be:	\$
refunded	
charged	\$

- a. ☒ A check in the amount of **\$710.00** to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **08-2789** A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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REGISTRATION NUMBER

15 NOVEMBER 2001

DATE

**SIMULTANEOUS IMAGE ACQUISITION USING MULTIPLE
FLUOROPHORE PROBE DYES**

BACKGROUND OF THE INVENTION

5 The subject invention relates generally to an improved scanner of the type that scans specimens for performing subsequent computer analysis on the specimens.

Micro array biochips are presently being used by several biotechnology companies for scanning genetic DNA samples applied to biochips into computerized images. These chips have small substrates with thousands of DNA samples that represent the genetic
10 codes of a variety of living organisms including human, plant, animal, and pathogens. They provide researchers with information regarding the DNA properties of these organisms. Experiments can be conducted with significantly higher throughput than previous technologies by using these biochips. Biochip technology is used for genetic expression, DNA sequencing of genes, food and water testing for harmful pathogens, and
15 diagnostic screening. Biochips may be used in pharmacogenomics and proteomics research aimed at high throughput screening for drug discovery.

DNA samples are extracted from a sample and are tagged with a fluorescent dye having a molecule that, when excited by a laser, will emit light of various colors. Often, a DNA sample is tagged with multiple dyes. Each of these dyes is utilized to illuminate
20 different characteristics of a particular DNA sample. These fluorescently tagged DNA samples are then spread over the chip. A DNA sample will bind to its complementary (cDNA) sample at a given array location. A typical biochip is printed with a two-dimensional array of thousands of cDNA samples, each one unique to a specific gene. Once the biochip is printed, it represents thousands of specimens in an area usually
25 smaller than a postage stamp.

A microscope collects data through a scanning lens by scanning one pixel of a specimen at a time. The scanning lens projects emitted light from the specimen onto a sensor that is manipulated along a predetermined pattern across the chip scanning an
entire biochip one pixel at a time. The pixels are relayed to a controller that sequentially
30 connects the pixels to form a complete, computerized biochip image. The fluorescent

dyes that are suitable for use in this capacity have spectral arrays that overlap when excited. The overlapping of the spectral arrays can skew the scanning results and can lead to inaccurate computer analysis of the DNA samples being scanned.

It would be desirable to perform scanning of DNA samples tagged with multiple dyes and yet prevent the overlap of the spectral arrays from adversely affecting data generated. Therefore, a need exists for an optical instrument capable of filtering the overlapping portions of the spectral arrays from multiple dyes while performing high speed scanning of current practice.

SUMMARY OF THE INVENTION AND ADVANTAGES

The present invention provides an optical instrument assembly that scans a DNA specimen one pixel at a time and relays the scan to a controller that connects the pixels forming a computerized biochip image of the specimen. The assembly includes a transmitter for emitting an optical signal having at least a first and a second spectral array.

A reflector directs the optical signal onto the specimen, which is treated with fluorescent dyes that are excited by the various spectral arrays in the optical signal. A detector includes an objective lens that focuses the emitted optical signal from the specimen onto a sensor. The sensor transmits the emitted optical signal to a controller one pixel at a time.

A first drive mechanism varies the position of the optical signal transmitted onto the specimen in a forward and reverse direction. A second drive mechanism varies the position of the specimen relative to the optical signal. In this manner, a complete scan of the specimen is performed and transmitted to a controller one pixel at a time.

The controller terminates detection of one of the spectral arrays while varying the position of the optical signal in the forward direction and terminates detection of the other spectral array while varying the position of the optical signal in the reverse direction. By detecting only one spectral array at a time, the problem of overlapping spectral arrays from multiple dyes is eliminated improving the accuracy of the computer analysis performed upon the DNA sample.

3
BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings wherein:

- 5 Figure 1 is a detailed view of an optical instrument of the present invention;
 Figure 2 is a plan view of a biochip specimen of the present invention showing the movement of the scanning objective lens;
 Figure 3 is a side view of the first drive mechanism;
 Figure 4 is a top view of the second drive mechanism.

10

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The optical instrument assembly of the present invention is generally shown in Figure 1 at 10. The assembly includes a transmitter 12 for emitting an optical signal 14. In the preferred embodiment, the transmitter 12 comprises a laser. Figure 1 shows three
15 transmitters 12a-c, each emitting an optical signal 14a-c having a different spectral array. Additional transmitters 12 may be introduced to the assembly 10 as needed.

- A reflector 30 directs the optical signal 14 onto a specimen 90. The reflector 30 includes a plurality of turn mirrors 32. Figure 1 shows three turn mirrors 32a-c corresponding to the same number of transmitters 12a-c. Each optical signal 14a-c is
20 reflected by the turn mirrors 32a-c into corresponding beam combiners 34a-c. The beam combiners 34a-c, known as dichroic filters, transmit light of one wavelength while blocking other wavelengths. The beam combiners 34a-c collect the individual optical signals 14a-c into a combined beam along a single path and direct the beam towards a beam splitting mirror 20. The beam splitting mirror 20 includes an opening 22 through
25 which the combined optical signals 14a-c travel. Subsequently, the combined optical signals 14a-c reflect off a ninety degree fold mirror 36 located immediately above a scanning objective lens 52, which focuses the combined optical signals 14a-c onto a section of the specimen 90. A first drive mechanism 50 varies the position of the combined optical signal 14a-c onto the specimen 90 as will be explained further
30 hereinbelow.

The specimen 90 is treated with a plurality of dyes having fluorescent properties when subjected to the optical signal 14a-c. The specimen 90, having been treated with the dyes, and illuminated with the optical signal 14, emits the optical signal 44 at a spectral array corresponding to the dye selected. Different dyes may be used to examine different specimen 90 properties. Multiple dyes may be used to examine different properties of the same specimen 90 simultaneously. Typically, at least a first dye and a second dye will be used. The first dye is chosen to be illuminated with optical signal 14a and emits optical signal 44a having a first spectral array, and the second dye is chosen to be illuminated with optical signal 14b and emits optical signal 44b having a second spectral array.

The assembly 10 includes a detector 40 with a sensor 42 for detecting a emitted optical signal 44 from the specimen 90. The emitted optical signal 44 reflects off the opposite side of the beam splitting mirror 20 through a plurality of beam splitters 38a-b to separate the emitted optical signal 44 into individual signals 44a-c corresponding to different spectral arrays from the various dyes. Each individual signal passes through an emission filter 46a-c and is focused by a detector lens 48a-c into a pinhole. The individual signals 44a-c proceed through the pinholes to contact individual sensors 42a-c. The sensors 42a-c are in communication with a controller 80 as will described in further detail hereinbelow.

As shown in Figure 2, the objective lens 52 is moved in forward and reverse directions along the x-axis of the specimen 90 collecting data in each direction. The specimen 90 does not move in the x direction. The specimen 90 is moved in the y direction incrementally each time a scan is about to be started in the x direction. In this manner, a rectangular zigzag scanning pattern is performed upon the specimen 90.

Figure 3 shows a first drive mechanism 50 that varies the position of the combined optical signal 14a-c on the specimen 90 in a forward and reverse direction. The first drive mechanism 50 preferably employs a galvanometric torque motor 54 to rotate a sector-shaped cam 56 over an angle between plus forty degrees and negative forty degrees. The circular portion of the cam 56 is connected to the carriage 58 via a set of roll-up, roll-off thin, high strength steel wires 66a-b. The scanning objective lens 52 is

attached to the carriage 54. The radius of the cam 56 is such that its rotation will cause the carriage 58 to travel a linear distance along a rail 60 commensurate with the length of the scan along the x-axis.

The controller 80 communicates with the transmitters 12a-c and the sensors 42a-c.

5 The sensors 42a-c relay to the controller 80 the emitted spectral arrays from the specimen 90 for the controller to reconstruct the computerized image of the DNA sample. The controller 80 is formatted to modify the scanning pattern to prevent the detection of overlapping spectral arrays, which would otherwise produce inaccurate computerized image of the DNA sample. When the first drive mechanism 50 drives the combined

10 optical signal 14a-c in the forward direction, information from the first dye will be acquired. When the first drive mechanism 50 drives the combined optical signal 14a-c in the rearward direction, information from the second dye will be acquired.

To exclude information from the second dye, the controller 80 will deactivate either the sensor 42b that reads the second dye, or the transmitter 12b that excites the

15 fluorescent properties of the second dye. Likewise, to exclude information from the first dye, the controller will deactivate either the sensor 42a that reads the first dye, or the transmitter 12a that excites the fluorescent properties of the first dye.

In order to produce an accurate computerized DNA image, the controller 80 must correlate the forward and rearward scans. In order to calculate an accurate correlation,

20 the distance between consecutive scan lines should be no more than forty percent of the height of the optical resolution of the optical system utilized by the assembly 10.

Figure 4 shows a second drive mechanism 70 employing a stepper motor 72 to drive a precision screw 74 in a known manner. A nut 76 on the screw 74 is attached to the carriage 58 so that any rotation of the screw 74 will cause the carriage 58 to move

25 along a linear rail 60. The carriage in turn is equipped with a tray 76 which includes retainers 78 to hold a specimen 90 slide in a position and orientation that is repeatable within an accuracy required by optical focus and alignment criteria. The rail 60 and the stepper motor 72 are attached to the frame of the second drive mechanism 70.

The first and second drive mechanisms 50, 70 transmit location information to the

30 controller 80. The controller 80 uses the location information to map the scan data

received from the sensors 42a-c. A scanning accuracy of one micron is required to accurately map the scan using data from both directions scanned on the x-axis.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of

words of description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims, wherein reference numerals are merely for convenience and are not to be in any way limiting, the invention may be practiced otherwise than as

specifically described.

CLAIMS

What is claimed is:

1. A method of scanning a specimen with an optical instrument comprising the steps of:
 - 5 applying a plurality of dyes to the specimen comprising at least a first dye having a fluorescence which when excited by a first optical signal emits a first spectral array and a second dye having a fluorescence which when excited by a second optical signal emits a second spectral array;
 - 10 projecting a plurality of optical signals onto a section of the specimen, said signals comprising at least a first signal for emitting the first spectral array and a second signal for emitting the second spectral array;
 - detecting fluorescence emitted from the section of the specimen;
 - moving the optical instrument and specimen in a forward and a reverse direction relative to each other for detecting fluorescence from different sections of the specimen;
 - 15 and
 - wherein said step of detecting fluorescence is defined by detecting fluorescence corresponding to one of the spectral arrays in the forward direction and detecting fluorescence corresponding to other of the spectral arrays in the reverse direction.
2. A method as set forth in claim 1 wherein said step of detecting fluorescence
20 is further defined by projecting only one of said spectral arrays in the forward direction.
3. A method as set forth in claim 2 wherein said step of detecting fluorescence is further defined by projecting only one of said spectral arrays in the reverse direction.
4. A method as set forth in claim 3 wherein said step of detecting fluorescence is further defined by scanning for only one of said spectral arrays in the forward direction.
- 25 5. An assembly as set forth in claim 4 wherein said step of detecting fluorescence is further defined by scanning for only one of said spectral arrays in the reverse direction.

6. An assembly as set forth in claim 5 including the step of correlating successive forward scans and reverse scans for forming a computerized image of the specimen.

7. An optical instrument assembly comprising:

a transmitter for emitting an optical signal having at least a first and a second spectral array onto a specimen treated with fluorescent dyes being excitable by said first and said second spectral array for emitting optical signal with different spectral arrays from said specimen;

a detector for detecting a emitted optical signal from the specimen;

a first drive mechanism for varying the position of said optical signal on the specimen in a forward and reverse direction; and

a controller capable of terminating detection of one of said spectral arrays while varying the position of the optical signal in the forward direction and of terminating detection of the other of said spectral arrays while varying the position of the optical signal in the reverse direction.

8. An assembly as set forth in claim 7 including a second drive mechanism for varying the position of the specimen relative to said optical signal.

9. An assembly as set forth in claim 8 wherein said transmitter includes at least a first laser for emitting said first spectral array and a second laser for emitting said second spectral array.

10. An assembly as set forth in claim 9 wherein said controller terminates power to one of said first laser and said second laser when said optical signal is moving in the forward direction and the other of said lasers when the optical signal is moving in the reverse direction.

11. An assembly as set forth in claim 10 wherein said detector includes at least a first sensor for detecting said first spectral array and a second sensor for detecting said second spectral array.

12. An assembly as set forth in claim 11 wherein said controller deactivates one of said first and said second sensors when said optical signal is moving in the forward direction and deactivates the other of said sensors when said optical signal is moving in the reverse direction.

13. An assembly as set forth in claim 12 wherein said first sensor and said second sensor are in communication with said controller for relaying to said controller detection of said first spectral array and said second spectral array emitted from the specimen.

14. An assembly as set forth in claim 13 wherein said controller correlates
5 detection of said first spectral array with detection of said second spectral array for forming a computerized image of the specimen.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78993 A1

(51) International Patent Classification⁷: C12Q 1/00, 1/68,
G01N 1/30, 21/64, 21/76, 33/53, G06K 9/00

(21) International Application Number: PCT/US00/16795

(22) International Filing Date: 16 June 2000 (16.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/139,991 18 June 1999 (18.06.1999) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

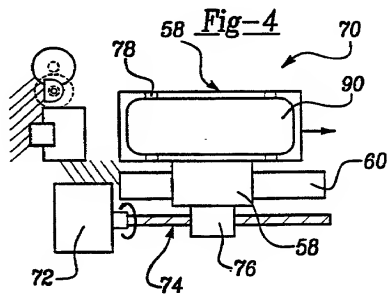
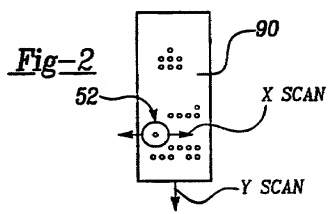
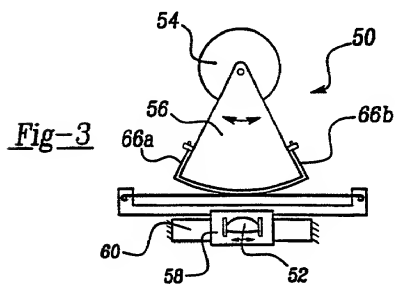
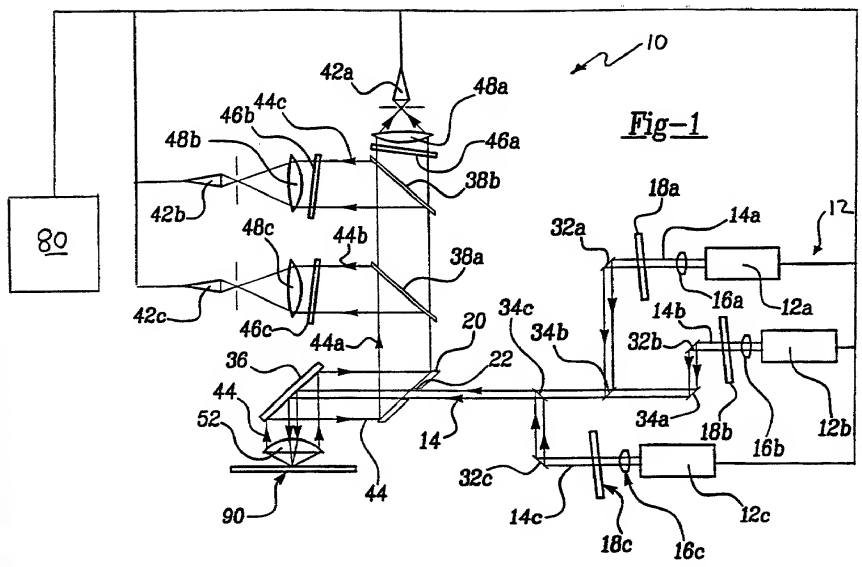
For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SIMULTANEOUS IMAGE ACQUISITION USING MULTIPLE FLUOROPHORE PROBE DYES

(57) Abstract: An optical instrument assembly for scanning biochips for DNA samples includes a transmitter for projecting an optical signal having at least a first and a second spectral array onto a DNA containing specimen. A detector includes a sensor for detecting an emitted optical signal from the specimen. A first drive mechanism varies the position of the optical signal on the specimen in a forward and a reverse direction. A second drive mechanism varies the position of the specimen relative to the optical signal. A controller terminates detection of one of the spectral arrays while varying the position of the optical signal in the forward direction and terminates detection of the other spectral array while varying the position of the optical signal in the reverse direction.

WO 00/78993 A1

09/980,836



**COMBINED DECLARATION AND POWER OF ATTORNEY**

As the below named inventors, we hereby declare: that our residences, post office addresses and citizenships are as stated near our names below; that we are joint inventors and we believe we are the original and first inventors of the subject matter of which is claimed and for which a patent is sought on the invention entitled

**SIMULTANEOUS IMAGE ACQUISITION USING
MULTIPLE FLOUROPHORE PROBE DYES**

which is described and claimed in the specification of which was filed on June 18, 1999 as United States Provisional Application Serial No. 60/139,991; attorney docket number 60,132-056 and that this application was filed on June 16, 2000 as International Application (PCT) No. PCT/US00/16795; attorney docket no. 60,132-069.

We have reviewed and understand the contents of this specification, including the claims, as amended by any amendment referred to above; that we do not know and do not believe the same was ever known or used in the United States of America before our invention thereof or patented or described in any printed publication, in any country before our invention thereof for more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application; that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by us or our legal representatives or assigns more than twelve (12) months prior to this application; that we acknowledge our duty to disclose information of which we are aware which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a); and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by us or our legal representatives or assigns except as follows:

PRIORITY CLAIM

We hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.58 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

APPLICATION NUMBER	DATE OF FILING (month, day, year)	STATUS
PCT/US00/16795	June 16, 2000	Pending



Atty Docket No. 60,132-083

Docket No. 60132-069

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of the foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application(s) for patent or inventor's certificate filed on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

Such applications have been filed as follows:

COUNTRY	APPLICATION NUMBER	DATE OF FILING (month, day, year)	PRIORITY CLAIMED UNDER 37 USC 119
USA	60/139,991	June 18, 1999	Yes <u>X</u> No _____

We hereby appoint Raymond E. Scott, Registration No. 22,981; Randall L. Shoemaker, Registration No. 43,118; Samuel J. Haidle, Registration No. 42,619; William H. Honaker, Registration No. 31,623; Harold W. Milton, Jr., Registration No. 22,180; Jeffrey A. Sadowski, Registration No. 29,005; David M. LaPrairie, Registration No. 46,295; Steven C. Wichmann, Registration No. 37,758; Gregory D. DeGrazia, Registration No. P-48,944; and James R. Yee, Registration No. 34,460 as our attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith. Please address all correspondence and telephone calls to:

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20060603 04:50Z



We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Dated: 4/18-01

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Dated: _____



Atty Docket No. 60,132-083

Docket No. 60132-069

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Dated: 04/03/2002